REMARKS

In this Amendment, Applicant has cancelled Claims 1 – 22 without prejudice or disclaimer, and added Claims 23 – 55. Claims 23 – 55 have been added to specify different embodiments of the present invention and overcome the rejection. In addition, the specification has been amended to correct translational, clerical and grammatical errors and rephrase certain expressions. It is respectfully submitted that no new matter has been introduced by the new claims and amended specification. All claims are now present for examination and favorable reconsideration is respectfully requested in view of the preceding amendments and the following comments.

REJECTIONS UNDER 35 U.S.C. § 112 FIRST PARAGRAPH:

Claim 1 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

It is respectfully submitted that the new claims have overcome the rejection and satisfy the written description requirement. More specifically, Claim 1 has been cancelled without prejudice or disclaimer. The rejection is moot. In addition, the new Claims 28 and its dependent claims, as well as other claims, have clear support in the specification, especially the examples. Thus, the new claims clearly define the invention that complies with the written description requirement.

Therefore, the rejection under 35 U.S.C. § 112, first paragraph has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112 SECOND PARAGRAPH:

Claims 1 – 22 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is respectfully submitted that the currently presented amendments clearly point out and define the embodiment of the present invention. More specifically, Claims 1 – 22 have been cancelled. Thus, the rejection to these claims is moot. In addition, Claims 23 – 55 have been added to clearly define the present invention as stated above. It is respectfully submitted that, the currently presented Claims 23 – 55 clearly define the invention.

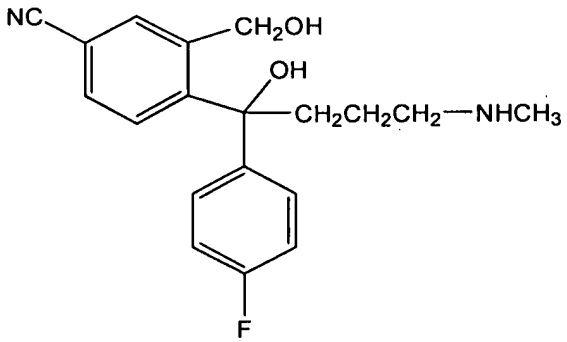
Therefore, the rejection under 35 U.S.C. § 112, second paragraph, has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 102:

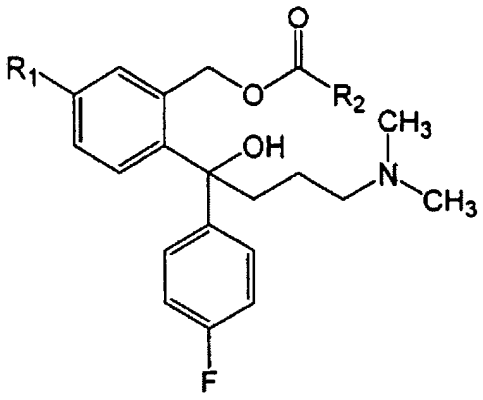
Claims 1 – 22 have been rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Li et al. (CN15110024, STN Accession Number; 2005:519249; Document Number: 143:59681), hereinafter CN15110024.

Applicant traverses the rejection and respectfully submits that the rejection is incorrect and the present-claimed invention is not anticipated by the cited reference. First, the present invention is directed towards obtaining the pure citalopram diol intermediate free base crystal through crystallizing the citalopram diol intermediate free base, then the free base reacts with a chiral organic acid in isopropanol to form a salt, which is crystallized and resolute. After being processed by a base, the S-citalopram diol intermediate free base is obtained, which is converted to S-citalopram. However, CN1510024 discloses citalopram diol intermediate free base in reaction with XCOR2, which forms a new compound – diol intermediate (see Formula B below). This new compound reacts with a chiral organic acid to form a salt, which is crystallized and separated. After being processed by a base, the new compound's S-enantiomer free base is obtained, which is a S-citalopram diol intermediate derivative. The obtained S-citalopram diol intermediate, after subjecting to hydrolysis, produces S-citalopram. Therefore, the processes and methods of the present invention and CN1510024 are significantly different.

Second, the claimed subject matter of the present invention includes the crystalline free base of citalopram diol intermediate, such crystal, which is shown as Formula A below, is new. CN1510024 disclosed the compound of Formula B. The compound of Formula B obviously does not include the compound of Formula A. B is a derivative of A, but different from A.



(A)



(B)

Third, the separation/resolution methods are different. The present invention uses citalopram diol intermediate free base of Formula A forming salts with an optically active acid, which is crystallized and resolute. However, in CN1510024, the compound of Formula B forms salts with an optically active acid, which is crystallized and resolute.

Thus, the claimed invention is completely different from the disclosed compounds and processes of CN1510024. The present invention discloses the purification of citalopram diol intermediate free base by making citalopram diol intermediate free base crystal. By using purified citalopram diol intermediate free base as a raw material, the pure citalopram or S-citalopram is conveniently obtained. The crystal of citalopram diol intermediate free base is a new type of crystal, or a new compound. The examples and drawings of the present invention disclosed two types of citalopram diol intermediate free base crystals. Before the priority date of the present invention, there was no prior art or any person predicting that a crystal of citalopram diol intermediate free base can be obtained, nor was there any prior art disclosing the method of obtaining a crystal of citalopram diol intermediate free base.

Therefore, the newly presented claims are not anticipated by Martin and the rejection under 35 U.S.C. § 102 (b) has been overcome. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102 (b) is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103:

Claims 1 – 22 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bogesco et al. (US 4,650,884) and James F. Norris, Experimental Organic Chemistry (1924, pages 3 – 4). Claims 2 – 22 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Peterson et al. (WO 2004/056745) in view of Bogesco.

Applicant traverses the rejection and respectfully submits that the embodiments of present-claimed invention are not obvious over the cited references. More specifically, Claims 1 – 22 have been cancelled without prejudice or disclaimer. The rejection to these claims is moot. In addition, new Claims 23 – 55 include the features that are significantly from those disclosed in cited references, individually or in combination.

First, the present invention is related to pure crystalline free base of 3-hydroxymethyl-4-[1-(4-fluorophenyl)-1-hydroxyl-4-(dimethylamino)] butylbenzonitrile and the method of purification thereof. This crystal is a new type of crystal. As stated above, Before the priority date of the present invention, there was no prior art or any person predicting that a crystal of citalopram diol intermediate free base can be obtained, nor was there any prior art disclosing the method of obtaining a crystal of citalopram diol intermediate free base.

In fact, it is very difficult to obtain citalopram diol intermediate free base in crystalline form. All prior art references only discloses citalopram diol intermediate free base in solution or as an oil substance. Usually, cooling or evaporating the saturated citalopram diol intermediate free base solution would only produce citalopram diol intermediate free base oil substance, not a crystal. Thus, in prior art, citalopram diol intermediate free base is usually purified, added acids to form salts. The obtained salts are crystallized and purified. Then they are converted to free base. It is very difficult to obtain pure citalopram diol intermediate free base crystal. To do so, it is very complex to

select proper solvent, temperature as well as other conditions for crystallization. Thus, it was not in the purview of a person of ordinary skill in the art.

Second, the present invention discloses the method of using citalopram diol intermediate free base to making highly pure citalopram. Such method is simple, low in cost and high in yield. There are many other methods concerning the preparation of citalopram. No matter which method is adopted, several impurities especially those having similar structures with the product are hard to eliminate. Many purification processes are required in order to obtain relatively purer product. Although there are several disclosed methods such as GB2356199 or WO03/072565 for purifying citalopram crude product, they may only effectively eliminate one or several of the impurities. In GB2356199, a short vacuum distillation is employed, which requires expensive equipments and complex operations. In WO03/072565, complex operations like several salt formation processes and several careful pH adjustments are required. These long purifying processes result in loss of the product while achieving limited success. Though a lot of purification processes which may result in the loss of citalopram are employed, the impurities especially those having identical structures with the product are hard to eliminate. It is well known that some of the impurities are from the early starting materials of citalopram or S-citalopram, such as different starting materials for 5-cyanophthalide. Due to the incomplete conversion of the early starting materials, those materials as well as the impurities which resulted from the conversion process have similar structures with the raw materials or intermediates of different stages. They will further be converted into the impurities which have similar structures with the ultimate product during the synthesis process of citalopram or S-citalopram (please refer to background section of the specification).

To the contrary, the present invention discloses a method of preparing crystal product of citalopram diol intermediate and its salt, through which, the product obtained is pure and with a good crystal form and the yield is high (chemical purity exceeds 99.8%). Citalopram diol intermediate free base is freed and precipitated in the form of crystal. The free base is subjected to crystallization one or more times to obtain the crystal. The crystal is further subjected to ring closure by dehydration to obtain citalopram. The obtained citalopram is further converted into citalopram salt.

Third, another aspect of the present invention is to use citalopram diol intermediate free base crystal for preparing pure citalopram diol intermediate free base

and its salt, which are used to make S-citalopram and its salt. It is well-known that citalopram has two enantiomers: S-citalopram and R-citalopram. It is S-citalopram that has the antidepressant activities; R-citalopram hardly has such activities. Therfore, a more effective and economical purification method is required for the industrial production of citalopram. Especially for the preparation of S-citalopram in particular, a more effective and simpler method is needed. Before resolution, the preferred chemical purity of citalopram diol intermediate alkali is over 99.8%, while after resolution, the purity of the enantiomer is over 99.9%.

Regarding US4650884, it discloses a method for making antidepressant citalopram. It did not mention the diol free base crystal or crystalline free base of the diol, nor did it mention an intention to convert the diol free base into diol free base crystal. Furthermore, it did not disclose a method or process to prepare the diol free base crystal. From the description and examples 1 – 2 on pages 3 – 5 of US4650884, it is clear that:

1. Example 1 discloses the diol free base intermediate in solvent and the diol free base oil substance. However, it was not solid, let alone a crystal.
2. In Example 1, when purifying the above mentioned diol free base, it used the method of adding hydrogen bromide into diethyl ether solution (see col 4, lines 21 – 25). The diol free base salt formed a salt in reaction with hydrogen bromide. A crystal is obtained after processing. Obviously, such crystal is the crystal of diol hydrogen bromide addition salt.
3. In addition, the wet cake obtained is recrystallized from water (1500ml) (see col. 4, lines 29 – 30). This further supports that crystal is the crystal of diol hydrogen bromide addition salt, NOT crystal of diol free base. Because the diol free base is not easily dissolved in water, this method clearly is not suitable for crystallizing the diol free base as claimed in the present invention.
4. Furthermore, the purified product is 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl) benzonitrile, hydrobromide with a yield of 425 g at MP 205°C - 206°C. It also contain 18.87% of Br. (see col. 4, lines 40 – 50). Thus, it is clear that Example 1 of US4650884 the crystal of diol hydrogen bromide addition salt, NOT crystal of diol free base as claimed in the present invention. It does not obtain the diol

free base crystal, nor does it disclose the process and method of preparing diol free base crystal.

5. In Example 2 of US4650884, it discloses toluene solution of above diol free base. The solution is the raw material for preparing citalopram, not for preparing diol free base crystal. It is well known that diol free base and diol addition salt are different substances, just like NH_3 and NH_4Cl. The crystalline diol free base (crystal of diol free base) and dissolved diol free base in solution are different substances. The crystalline diol free base has its melting point and crystal constant, etc.

The present invention discloses a method of preparing crystal product of citalopram diol intermediate and its salt, through which, the product obtained is pure and with a good crystal form and the yield is high (chemical purity exceeds 99.8%). Citalopram diol intermediate free base is freed and precipitated in the form of crystal. The free base is subjected to crystallization one or more times to obtain the crystal. The crystal is further subjected to ring closure by dehydration to obtain citalopram. The obtained citalopram is further converted into citalopram salt. In addition, another aspect of the present invention is to use citalopram diol intermediate free base crystal for preparing pure citalopram diol intermediate free base and its salt, which are used to make S-citalopram and its salt and may also be used for resolution. Before resolution, the preferred chemical purity of citalopram diol intermediate alkali is over 99.8%, while after resolution, the purity of the enantiomer is over 99.9%. None of US4650884, James F. Norris, or Peterson et al. (WO 2004/056745) alone or in combination discloses the above features. According to MPEP 2143.01, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The general statement in James F. Norris would not provide the suggestion to a person of ordinary skill in the art on the desirability or practicability of obtaining diol free base crystal. As stated above, it is very difficult to obtain such crystal prior to the present invention.

In summary, there are significant differences between the pending claims and cited references. There is no motivation or suggestion for success of the combination of these references. Therefore, even if the cited references are combined, they do not teach or suggest the present invention as defined in Claims 23 – 55.

Therefore, the pending claims are not obvious over the cited references. The rejection under 35 U.S.C. § 103 has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 103 is respectfully requested.

Having overcome all outstanding grounds of rejection, the application is now in condition for allowance, and prompt action toward that end is respectfully solicited.

Respectfully submitted,

JACOBSON HOLMAN PLLC

Date: January 10, 2008
(202) 638-6666
400 Seventh Street, N.W.
Washington, D.C. 20004
Atty. Dkt. No.: P71315US0

By _____
John C. Holman
Registration No. 22,769

Enclosures:

Substitute Specification
Mark-up Specification Showing Changes Made